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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	9

DATE MAILED: 01/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/616,223	NADEL ET AI	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *4-9,11 and 20-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,10,12-19 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3 & 4* .
4) ☐ Interview Summary (PTO-413) Paper No(s) _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office action is in response to the communication filed October 1, 2001, Paper No. 7.

Claims 1-26 are pending in the instant application.

Claim Objection

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 15 (the second claim 15) and 24 (the second claim 24) have been renumbered 16 and 25 respectively.

Election/Restriction

Applicant's election with traverse of Group I, claims 1-3, 10, 12-19 and 26 in Paper No. 7 is acknowledged. The traversal is on the ground(s) that examination of the entire application can be made without a serious burden to the examiner. This is not found persuasive because the instant application contains claims which are drawn to different and distinct inventions, which in turn require very different searches and considerations.

The requirement is still deemed proper and is therefore made FINAL.

Claims 4-9, 11, 20-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and 3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 2, lines 2-3, the term "selective for EGF-R" is vague and indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 10, 12-19 and 26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is drawn to compositions and methods comprising the administration of any epidermal growth factor receptor (EGF-R) antagonist, including BIBX1522. The specification and claims do not indicate what distinguishing attributes are concisely shared by the members of the genus comprising EGF-R antagonists. The specification and claims do not describe elements which are essential to the genus comprising such antagonists. Thus, the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between members of the genus is premitted. Concise structural features that could distinguish structures or compounds within this genus from others are missing from the instant disclosure. Furthermore, no identifying structural features have been set forth to describe the compound BIBX1522. The general knowledge and level of skill in the art do not supplement the omitted description of this broad genus, which includes BIBX1522. The specification fails to teach or adequately describe a representative number of species in this broad genera such that the common attributes or characteristics concisely identifying members of the genus are exemplified, and, because the claimed genus is so highly variant, the description provided is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus claimed. Thus, Applicant was not in possession of the claimed genus.

Claims 1-3, 10, 12-19 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing goblet cell hyperplasia in an airway of an individual comprising the administration of the EGF-R antagonist BIBX1522 prior to induction of EGF-R, does not reasonably provide enablement for methods of reducing goblet cell hyperplasia in an individual's airway or treating nasal polyps comprising the administration of any EGF-R antagonist via any mode of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of reducing goblet cell hyperplasia in an individual's airway comprising the administration of any epidermal growth factor receptor (EGF-R) antagonist to a patient suffering from airway hypersecretion of mucus due to airway goblet cell hyperplasia. The claims are also drawn to methods of treating nasal polyps comprising the administration of any EGF-R antagonist to an individual suffering from nasal polyps.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The nature of the invention. The claims read on methods of treating either goblet cell hyperplasia in the airway of an individual or of treating nasal polyps in an individual comprising the administration of any antagonist to EGF-R. EGF-R antagonists encompass a wide range of compounds, including heterocyclic compounds which inhibit tyrosine kinases as described previously by Fraley et al (See USPN 6,306,874), and which further include inhibitors of the

expression of EGF-R (i.e. antisense), as well as including the compounds described more specifically in the instant specification, such as BIBX1522. Examples have been provided in the instant application for the ability of BIBX1522 to inhibit EGF-R in its ability to induce mucin expression in goblet cell proliferation.

The state of the prior art and the predictability or unpredictability of the art. Insofar as the claims are interpreted as encompassing the administration of inhibitors of EGF-R expression (i.e. via antisense), Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.) Insofar as the claims are interpreted as encompassing the administration of EGF-R antagonists such the heterocyclics disclosed by Fraley et al in USPN 6,306,874, the same unpredictability exists in being able to determine the best mode of

application of such compounds to an organism for their ability to reduce goblet cell proliferation or nasal polyps by inhibiting or antagonizing EGF-R.

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of treating nasal polyps or reducing airway goblet cell hyperplasia in an organism comprising the administration of any antagonist of EGF-R . The specification teaches the reduction in MUC5AC synthesis in goblet cells in vitro and in vivo comprising the administration of BIBX1522 prior to induction of goblet cell hyperplasia (and prior to EGF-R induction) via various means, including degranulation via inhalation of fMLP, exposure of cells or rats to cigarette smoke, IL13 induction, tracheal instillation of agarose plugs into rats, and administration of EGF or TNF-alpha. The specification fails to teach the successful delivery of any and/or all antagonists of EGF-R to an organism whereby airway goblet cell hyperplasia is reduced and further whereby treatment effects are provided for nasal polyps. One skilled in the art would not accept on its face the examples given in the specification of pretreatment with BIBX1522 (i.e. before goblet cell hyperplasia induction occurs in an organism) as being correlative or representative of the administration of any and/or all antagonists of EGF-R in an organism whereby treatment effects are provided and airway goblet cell hyperplasia is reduced in view of the lack of guidance in the specification and known unpredictability associated with the administration and appropriate in vivo delivery of any and/or all EGF-R antagonists whereby treatment effects are provided. The specification as filed fails to provide any particular guidance

which resolves the known unpredictability in the art associated with in vivo delivery and treatment effects provided by any EGF-R antagonist administered. Nor is any guidance provided for resolving the known unpredictability in the art associated with the treatment effects provided by the known BIBX1522 antagonist after goblet cell hyperplasia has been induced.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to methods of reducing goblet cell hyperplasia in an individual's airway comprising the administration of any epidermal growth factor receptor (EGF-R) antagonist to a patient suffering from airway hypersecretion of mucus due to airway goblet cell hyperplasia. The claims are also drawn to methods of treating nasal polyps comprising the administration of any EGF-R antagonist to an individual suffering from nasal polyps. In order to practice the invention over the scope claimed, it would require undue trial and error and undue experimentation beyond which is taught in the specification to practice the invention drawn to any route of administration of any EGF-R antagonist to an organism such that airway hypersecretion of mucus due to airway goblet cell hyperplasia is inhibited and further whereby treatment effects are provided for nasal polyps. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring EGF-R such that any and/or all antagonists successfully inhibit EGF-R and further whereby treatment effects are provided in an organism. Since the specification fails to provide any particular guidance for the successful delivery of such a broad array of compounds

(i.e. encompassing any and/or all EGF-R antagonists) in an organism, and since determination of these factors for a particular inhibitor or antagonist of EGF-R is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

December 13, 2001

ANDREW WANG
PRIMARY EXAMINER